



## Scientific Abstract

### **SU2C-Torrey Coast Foundation Gastroesophageal Cancer Research Team:**

### **“Targeting Immune Evasion in Gastroesophageal Cancer”**



Recently, clinical trials led by members of our team have led to the FDA approval of combined immune checkpoint blockade (ICB) and chemotherapy for metastatic gastroesophageal cancer (GEC), and of ICB, chemotherapy, and HER2-directed therapy for HER2+ disease. Although these combinations provide unprecedented benefit for some patients, the majority do not meaningfully respond. This limited efficacy likely relates to ongoing chromosomal instability (CIN), which characterizes most GECs (up to 70% of advanced cases) and is associated with lower intratumoral T cell infiltration, ICB response rates, and overall survival. Whether CIN drives immune evasion through defects in antigen presentation, the quality or quantity of tumor neoantigens, or defects in innate and adaptive immune signaling remains poorly understood. This Research Team will define the immune-suppressive mechanisms contributing to ICB resistance in GEC and their relationship to CIN. Specifically, the research aims to delineate subtype-specific features of the pre-treatment tumor neoantigens and tumor immune microenvironment (TME) associated with clinical benefit from ICB and their relationship to CIN as well as assess the potential of cGAS+ micronuclei, an indicator of ongoing CIN, as a biomarker of ICB resistance. Finally, the Team will identify neoantigens in CIN tumor biopsies and evaluate the prevalence of corresponding T cells. This project promises to revolutionize understanding of the immunobiology of GEC, leading to critical insights that will inform the next generation of immunotherapies.

